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Enantioselective Total Syntheses of Kuwanon X, Kuwanon Y, and Kuwanol A

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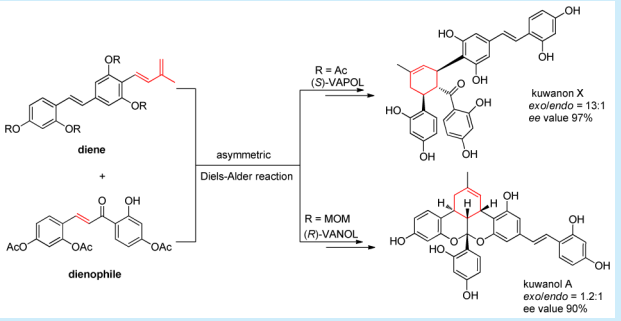
Supporting Information

ABSTRACT: The first enantioselective total syntheses of (−)-kuwanon X, (+)-kuwanon Y, and (+)-kuwanol A have been accomplished by using asymmetric Diels−Alder cycloaddition promoted by chiral VANOL or VAPOL/boron Lewis acid. The biosynthesis-inspired asymmetric Diels−Alder cycloaddition shows high *exo* selectivity (*exo*/*endo* = 13/1), which was unprecedented in the previous total syntheses of related prenylflavonoid Diels−Alder natural products. An acid catalyzed intramolecular ketalization process enabled a biomimetic transformation to construct the polycyclic skeleton of kuwanol A efficiently.



About 50 kinds of optically active Diels−Alder type natural products have been isolated from the moraceous plant whose root bark has been used as a traditional Chinese medicine for antiphlogistic, expectorant, antipyretic, and diuretic purposes.[1] Some of them, as bioactive plant constituents, showed promising biological activities such as antibacterial, hypotensive, antiphlogistic activities, etc.[2] Structurally, these molecules share the same chalcone dienophile moiety but differ in the dehydroprenyl diene moiety. Based on the structure of diene, the Diels−Alder type adducts from the moraceous plant can be divided into five structural categories.[1b,3,4] Due to their promising biological activities and striking chemical structures, the Diels−Alder type natural products represent very attractive synthetic targets, and efforts have been made toward the total syntheses of three categories of the adducts.[4]

Representative Diels−Alder type adducts of a chalcone and a dehydroprenylstilbene, one group of adducts from the moraceous plant, are shown in Figure 1: kuwanon X (**1**),[5] kuwanon Y (**2**),[6] kuwanol E (**3**),[7] and the related ketalized adducts kuwanol A (**4**)[8] and sorocein I (**5**).[9] To date no total syntheses of this type of natural products have been reported, although some of them have shown promising biological activities.[10] For example, the kuwanol E is one of the most potent natural compound inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B (K_i = 1.6 ± 0.1 μM) discovered by far.[10c]

Although many methods[11] have been developed to synthesize Diels−Alder type adducts or their derivatives, the enantioselective total syntheses of these natural products are very limited. Recently, an asymmetric Diels−Alder cycloaddition, catalyzed by chiral VANOL or VAPOL-boron Lewis acid, has been reported

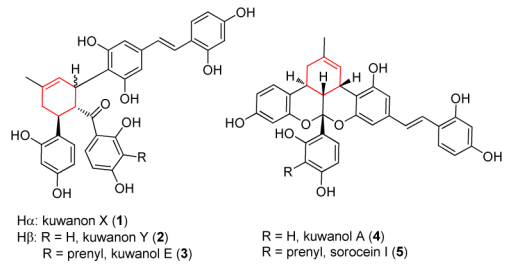


Figure 1. Representative Diels−Alder type adducts of a chalcone and a dehydroprenylstilbene.

to construct the desired cyclohexene skeleton by our group.[12a,b] In our continuous efforts to synthesize the different Diels−Alder type adducts from different categories, herein we would like to report the first enantioselective total syntheses of kuwanons X and Y, and kuwanol A.

As depicted in Scheme 1, the kuwanol A (**4**) could be derived from the *endo*-kuwanon Y (**2**) through a biomimetic acid catalyzed ketalization.[6] The kuwanons X (**1**) and Y (**2**) could be generated through asymmetric Diels−Alder cycloadditions from the known dienophile **6**[13] and diene **7**. For the synthesis of diene **7**, the dehydroprenyl group could be introduced by palladium catalyzed cross-coupling reaction from iodide **8** in which C−C double bond could be constructed by Horner−Wadsworth−Emmons reaction from phosphonate **9** and aldehyde **10**.

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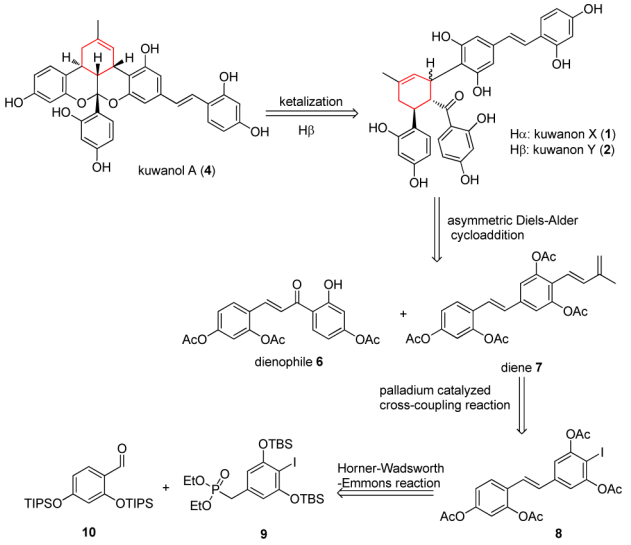
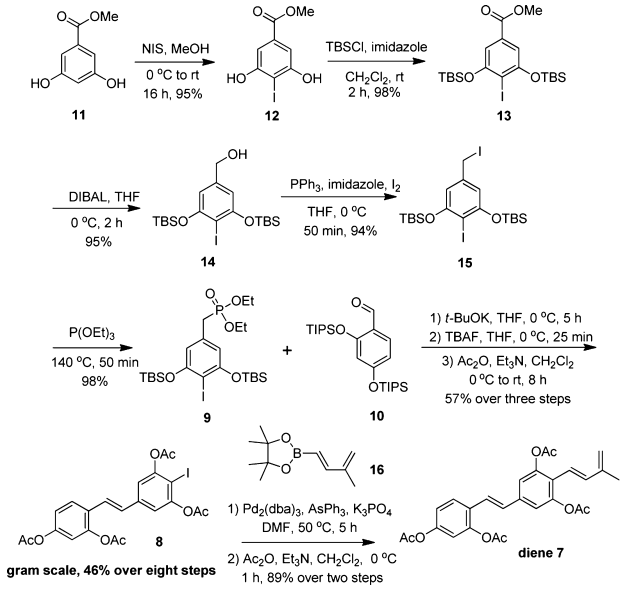
Scheme 1. Retrosynthetic Analysis of Kuwanon X, Kuwanon Y, and Kuwanol A



As shown in Scheme 2, the synthesis of diene **7** commenced with iodination of methyl 3,5-dihydroxy-benzoate **11** to give

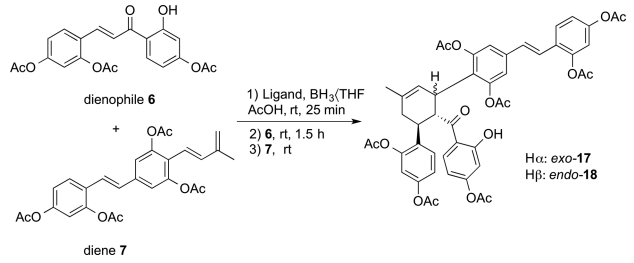
Scheme 2. Synthesis of the Diene 7



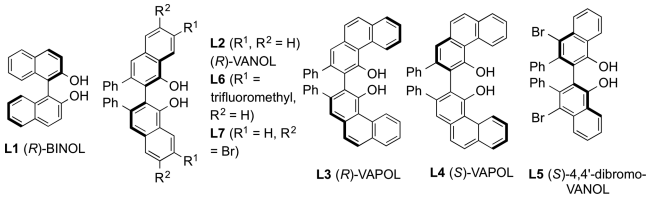
iodide **12** in 95% yield. Compound **12** was protected with TBS group to give **13**, then reduced by DIBAL to afford alcohol **14**, iodinated to give iodide **15** and followed by reacting with triethyl phosphite to afford **9** in high yield over four steps. Iodide **8** was obtained in 57% yield over three steps by Horner–Wadsworth–Emmons reaction followed by deprotection of the silyl protecting groups and reprotection with acetyl groups. With iodide **8** in hand, first we tried to prepare diene **7** by Heck reaction with 2-methylbut-3-en-2-ol and dehydration[11f] (not shown). Unfortunately, only a mixture was obtained. Alternatively, Suzuki reaction was used to synthesize diene **7**.[11c,14] Diene **7** could not be obtained in satisfying yield by Suzuki reaction in one step, though acetyl reprotection of the crude mixture gave diene **7** in 89% yield.

With diene **7** and dienophile **6** in hand, attention was turned to the asymmetric Diels–Alder cycloaddition. As shown in Table 1,

Table 1. Screening of Chiral Ligands for the Asymmetric Diels–Alder Cycloaddition



entry	ligands	time (h)	yield (%)	*endo*/*exo*[a]	*ee* (%)[b] *endo*/*exo*
1	**L1**	23	95	1:4.2	70/13
2	**L2**	24	70	1:5.3	94/81
3	**L3**	21	69	1:11.4	50/96
4	**L4**	21	79	1:13.0	53/97
5	**L5**	22	60	1:3.1	0/1
6	**L6**	20	42	1:7.0	81/63
7	**L7**	28	80	1:3.5	96/63



[a]Based on ^{1}H NMR analysis. [b]Determined by chiral HPLC analysis.

(*R*)-BINOL (**L1**), (*R*)-VANOL (**L2**), and (*R*) and (*S*)-VAPOL (**L3** and **L4**) were initially used to catalyze the reaction. All of these chiral boron complexes showed unexpected *exo* selectivity[15] (entries 1–4). Among them, **L4** effectively catalyzed the Diels–Alder cycloaddition with very high *exo* selectivity (*exo*/*endo* = 13/1) and *ee* value (97%), which could be used directly for the enantioselective total synthesis of **1** (entry 4). For the enantioselective synthesis of **2**, using **L2** as chiral ligand gave a satisfying *ee* value but not a good *endo*-selectivity (entry 2). Then several VANOL derivatives were used to improve the *endo*-selectivity (entries 5–7). The (*S*)-4,4′-dibromo-VANOL (**L5**) had the biggest negative impact on the enantioselectivity, which was consistent with the previous results.[12a,16] (entry 5). Compared with **L2**, the (*R*)-7,7′-ditrifluoromethyl-VANOL (**L6**) gave worse *endo*-selectivity and enantioselectivity (entry 6), while (*R*)-6,6′-dibromo-VANOL (**L7**) exhibited satisfying enantioselectivity and improved *endo*-selectivity (entry 7). A proposed transition state to explain the Diels–Alder selectivity has been reported by our previous study[12b] and is also included in the Supporting Information.

The corresponding *exo*-**17** and *endo*-**18** were treated with K_2CO_3 in the mixture of THF and MeOH to give **1** and **2** in yields of 67% and 49%, respectively, as shown in Scheme 3. The spectroscopic data for synthetic **1** and **2** were in agreement with those reported for the natural products. With **1** and **2** in hand, sulfuric acid was employed to catalyze the biomimetic intramolecular ketalization of *exo*-**1** and *endo*-**2**, but only *endo*-**2** formed a ketalized product (see Supporting Information for detailed mechanism), which was confirmed as kuwanol A (**4**).

Although the enantioselective total synthesis of the ketalized compound **4** was accessible by using *R*-VANOL as a chiral ligand,

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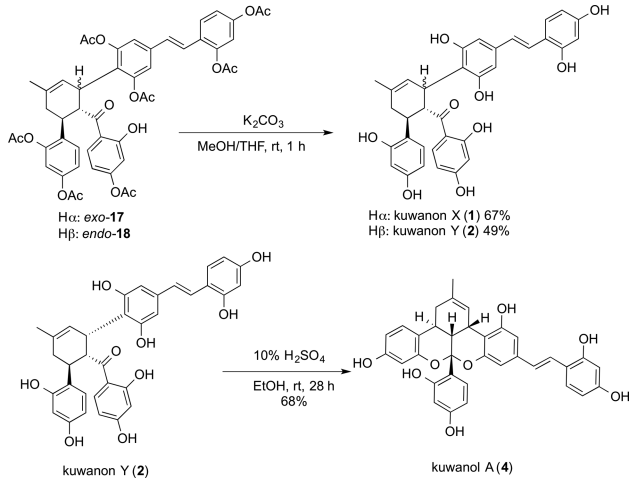
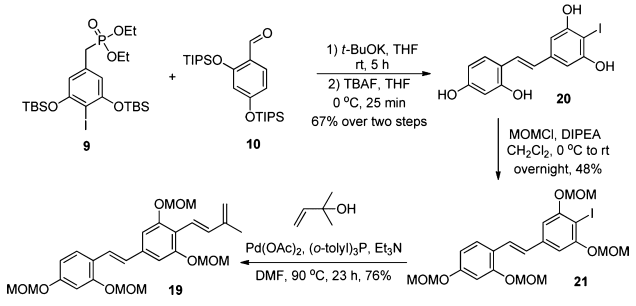
Scheme 3. Syntheses of Kuwanon X, Kuwanon Y, and Kuwanol A



the total yield from dienophile **6** was very low (3.7% over three steps) due to the low *endo*-selectivity and moderate yield in the subsequent two steps. As previously reported,[11c,f,g] when the two phenolic hydroxyl groups in the *ortho* position of the dehydroprenyl group were protected by MOM or Me group instead of acetyl group, no obvious *exo*/*endo* stereoselectivity was observed in the Diels–Alder cycloaddition. This inspired us to further investigate whether the two acetyl groups near the dehydroprenyl group played a key role in the *exo*-selectivity. MOM-protected diene **19** was synthesized from phosphonate **9** and aldehyde **10** as shown in Scheme 4. Iodide **21** was obtained

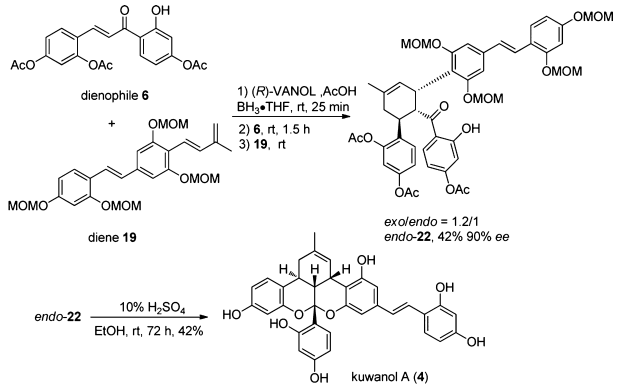
Scheme 4. Syntheses of the MOM Protected Diene



from precursors **9** and **10** after three steps. With iodide **21** in hand, commercially available 2-methyl-but-3-en-2-ol was again tested to synthesize diene **19** by Heck reaction and dehydration.[17] After screening several conditions, diene **19** could be obtained in 76% yield directly from 2-methylbut-3-en-2-ol.

With MOM protected diene **19** in hand, the asymmetric Diels–Alder cycloaddition promoted by (*R*)-VANOL (**L2**)/boron Lewis acid was achieved as shown in Scheme 5. Compared with the acetyl protected diene **7** (Table 1, entry 2), when diene **19** was used, the *endo*/*exo* stereoselectivity was changed from 1/5.3 to 1/1.2 without losing the enantioselectivity (from 94% to 90%). This indicates that different substitution in diene may contribute to different stereoselectivity in the asymmetric Diels–Alder cycloaddition.[15k,18] With the raised HOMO in diene **19**, the cycloaddition transition state occurs earlier in the reaction pathway; hence, there is less steric demand one would need to overcome for the *endo* transition state in comparison to the *exo*

Scheme 5. Synthesis of Kuwanol A from MOM Protected Diene 19



transition state, and so the subtle improvement to 1.2/1 was possible.[19]

In the next step, several acidic conditions such as 0.8 M HCl in THF/*i*-PrOH and 0.8 M sulfuric acid in EtOH were evaluated for one-pot deprotection and ketalization of *endo*-**22** but all failed. Ultimately we found deprotection/ketalization of **22** could be achieved in one step to afford **4** by using 10% sulfuric acid/EtOH. By changing the protecting group in the diene moiety, the total yield of kuwanol A (**4**) increased from 3.6% to 17.6% from the same dienophile **6** with one step shorter and no significant change in enantioselectivity.

In summary, the first enantioselective total syntheses of kuwanons X and Y and kuwanol A have been accomplished by employing a chiral ligand/boron Lewis acid promoted asymmetric Diels–Alder cycloaddition in 12 and 11 steps, respectively. The asymmetric Diels–Alder reaction featured high *exo*-selectivity. The synthesis also featured a biomimetic acid-catalyzed intramolecular ketalization process to furnish the striking polycyclic framework of kuwanol A in one step. Demonstrated by total syntheses of kuwanons X and Y and kuwanol A, the chiral ligand/boron Lewis acid catalyzed asymmetric Diels–Alder cycloaddition will have a broad application in the total syntheses of other related complex natural products isolated from moraceous plants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03285.

Experimental procedures, product characterizations, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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